REMARKS

Amendments

The cross-reference section of the specification is amended to reference the issued parent patent. Claim 2 is incorporated in claim 1 and therefore is cancelled as moot. Claim 3 is amended because of the amendment to claim 1. New claims 15-18 find support on page 58, lines 27-28, for example. Claim 19 finds support in claim 1 and on page 58, lines 27-28 combined with page 20, lines 9-11 which identifies lymphoma and leukemia cancer, for example. Claim 20 is supported on page 6, lines 5-6 and page 28, lines 24-25. In that the amendments do not add new matter, entry thereof is respectfully requested.

35 U.S.C. § 102(e)

Claims 1-4, 8-11 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 6,528,624 ("the '624 patent"). The Examiner relies on the disclosure in Table 3 and column 42 of the '624 patent concerning making and using of a polypeptide variant comprising a human IgG Fc region comprising amino acid substitutions at positions including 333 or 334 in rejecting the identified claims. In addition the Examiner references column 5, lines 37-41 of the '624 patent as teaching that the variant polypeptides can be used in treating a mammal comprising administering a therapeutically effective amount of the variants.

Applicant respectfully traverses this rejection.

First, Applicant points out that Example 3 in columns 41-44 of the '624 patent – in which is contained Table 3 – was first included in provisional application no. 60/116,100 filed January 15, 1999 ("the '100 application"), the second provisional to which the '624 patent claims priority. The claims of the present application are supported by provisional application no. 60/116,023 ("the '023 application") to which the present application claims priority. The '023 application was, like the '100 application, filed on January 15, 1999. Hence, the disclosure in Table 3 and column 42 of the '624 patent is not prior art to the present patent claims.

Second, as to the disclosure relied on in column 5, lines 37-41 of the '624 patent, while that is contained in an earlier provisional to which the '624 patent claims priority,

the variant to be administered "binds FcγRI, FcγRII, FcγRIII and FcRn but does not activate complement and comprises an amino acid substitution at amino acid position 270, 322, 329 or 331." The '624 patent in column 5, lines 37-41 cited by the Examiner does not refer to therapy with a variant which "mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively than the parent polypeptide" as recited in the present claims. Hence, Applicant submits that this second part of the '624 patent disclosure relied on does not teach the presently claimed method, and therefore does not anticipate the claims under 35 USC Section 102(e).

Reconsideration and withdrawal of the Section 102(e) rejection is requested in view of the above.

35 U.S.C. § 112, First Paragraph - Enablement

Claims 1-11 and 14 are rejected under 35 U.S.C. § 112 as failing to comply with the enablement requirement.

The enablement rejection, as it is understood by Applicant, has two main components: (1) the Examiner contends that the specification fails to enable a method for treating a disorder in a patient using polypeptide variants (pages 3-4 of the Office Action); and (2) the Examiner argues that the specification does not enable polypeptides, other than antibodies, in the method (page 5 of the Office Action). Applicant will address each of these below.

Applicant addresses first the issues raised by the Examiner as to the enablement of the presently claimed therapeutic method.

The Examiner argues that the specification only provides *in vitro* assays using antibodies to determine whether a particular variant is effective in ADCC, and states that it is not clear that reliance on the *in vitro* evidence of enhanced ADCC or even animal models accurately reflects the clinical efficacy of the antibody variants. The Examiner relies on Eccles *et al. Breast Cancer Res.* 3:86-90 (2001) as teaching that there is no formal proof that ADCC operates in patients, and some monoclonal antibodies that perform well in ADCC assays *in vitro* fail in clinical trials (page 88, lines 5-16 of the second paragraph in the right column is cited).

Applicant submits that the presently claimed therapeutic method is enabled. Claim 1 refers to a "method for treating a disorder in a mammal comprising administering to the mammal a therapeutically effective amount of" the variant. While the variant administered "mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively than the parent polypeptide," the claim does not *require* that ADCC be formally proven in a patient, such could be evaluated using, for example, the assays described in the present application. (The Examiner agrees, page 3 of the Office Action, that variants with greater ADCC activity towards breast tumor cells in the presence of effector cells isolated from normal human volunteers are enabled by the application). Applicant submits that one could practice the presently claimed therapeutic method without having to formally demonstrate that ADCC was operating in the patient. For example, the antibodies Rituxan® and Herceptin® discussed in Eccles *et al.* are indeed therapeutically effective antibodies approved by the Food and Drug Administration (FDA) for cancer therapy (see Introduction on page 86 of Eccles *et al.*), despite Eccles' qualms that their ADCC function may not have been formally proven in patients. In other words, the skilled artisan can practice the therapeutic method of the claims herein, without having to actually demonstrate ADCC function in a patient. Moreover, Eccles does agree that even though the importance may vary, "host mechanisms clearly can contribute to mAb-induced therapeutic response" (emphasis added, page 88 column 2, second full paragraph of Eccles *et al.*).

Addressing now the Examiner's reliance on another statement by Eccles *et al.* that "some mAbs that perform well in ADCC assays fail in clinical trials," Applicant submits that, at the time of filing the present application in 1999, a genus of therapeutic antibodies had been shown to have efficacy for treating a disorder in a mammal. Amongst those antibodies were Rituxan® and Herceptin® referenced in Eccles *et al.* Those prior art antibodies represent examples of antibodies for which variant forms could be made and used to treat a mammal according to the teachings in the present application. Moreover, other antibody variants could have been made and used to treat mammals based on the guidance in the present application. Even though some experimentation would be

necessary, such would not constitute undue experimentation given the body of knowledge in the field that was available at the filing date.

In summary then, Applicant submits that, at best, the statements on page 88, lines 5-16 of Eccles *et al.* merely represents one scientists' opinions about a feature which is not recited in the present claims - namely ADCC in human patients. Even then, her conclusions are merely that it hasn't been "formally" proven and that "some" mAbs may fail in clinical trials. Such does not represent evidence of nonenablement according to the enablement requirements of 35 USC Section 112. If anything, Eccles' recognition that antibodies such as Rituxan® and Herceptin® are therapeutically effective supports the patentability of the present claims.

The Examiner further relies on page 89, lines 12-15 of the left hand column of Eccles *et al.* as teaching that the specificity of binding of Ig isotypes to different FcR isoforms is complex with both CH2 regions and CH2/CH3 interface being implicated. Again, Applicant submits that such a statement fails to show that the presently claimed method will not work. Certainly, this does not to provide evidence that the claims are not enabled according to the provisions of 35 USC Section 112, first paragraph. Indeed, in spite of such asserted "complexity," a genus of therapeutic antibodies including Rituxan® and Herceptin® were known at the time of filing to be effective for therapy of disorders in mammals at the time of filing. Variant forms of such antibodies, and other antibodies, could have been made and used in the presently claimed method, without undue experimentation.

Applicant now addresses the Examiner reliance on Tutt *et al. J. Immunol.* 161: 3176-3185 (1998).

Relying on the title, the Examiner is of the view that Tutt *et al.* shows that in monoclonal antibody therapy of B cell lymphoma, the signaling activity on tumor cells appears more important that the recruitment of effectors. Applicant submits that Tutt's title is insufficient evidence to show the claims are not enabled according to the provisions of 35 USC Section 112, first paragraph. Tutt merely suggests signaling activity "appears" "more important." Indeed Tutt recognizes that others skilled in the art consider ADCC to be of "critical importance in determining clinical outcome" and that ADCC-active mAb have usually performed better in animal immunotherapy" (Tutt *et al.*

page 3176, right hand column). Plus, *even if*, signaling activity on tumor cells is more important, even the title of Tutt does not conclude ADCC is unimportant, just less important.

In any event, as noted above, the claims herein do not require that the antibody variant be proven to have ADCC function in a patient; the improved ADCC function of the variant can be assessed in assays such as those described in the present application. Hence, Applicant submits that, based on the guidance provided by the present application, the skilled person can make variant forms of therapeutic antibodies, such as those identified in Tutt *et al.* - including CD20 mAbs and CD52 mAbs (column 1 on page 3176), or anti-Id, anti-CD19 and anti-CD40 antibodies which were "therapeutically effective in vivo" (abstract) – and use such variant antibodies in the presently claimed method without having to exercise undue experimentation. Indeed, Applicant submits that Tutt *et al.* supports the patentability of the presently claimed method by showing that a genus of therapeutically useful antibodies were available for alteration and use in the presently claimed method.

The Examiner also relies on Tutt *et al.* as stating on page 3180, lines 16-18 of the right column that antibodies showing binding and cytotoxic activity against mouse B cell tumor *in vitro* do not seem to be effective *in vivo*. In the cited section, Tutt states, emphasis added, that "within these models, none of the in vitro assays (cytotoxicity or growth arrest) had indicated which mAb would be effective in vivo; therefore additional experiments were undertaken in vivo to investigate how therapeutic mAb control lymphoma growth." Hence, Applicant submits that the quoted statement in Tutt is specific to the A31 and BCL_1 models studied, and that further experiments were needed. Moreover, Tutt recognizes that other skilled artisans consider ADCC to be of critical importance in determining clinical outcome, and that ADCC-active mAb have usually performed better in animal immunotherapy (page 3176, right hand column).

Hence, Applicant submits that neither Eccles nor Tutt provides evidence of lack of enablement of the presently claimed invention. Applicant submits that the presently claimed method of treating an mammal with an antibody variant is enabled by the present disclosure. Reconsideration and withdrawal of the first component of the enablement rejection, relating to a therapeutic method, is respectfully requested.

Applicant turns now to the second component of the enablement rejection, namely the enablement of polypeptides other than antibodies. Without acquiescing in this basis of the rejection, and in order to expedite prosecution, claim 2 concerning antibody variants has been incorporated in claim 1, thus obviating this aspect of the enablement rejection.

Applicant now addresses the Examiner's statement on page 4 of the Office Action, that "the specification does not reasonably provide enablement for a method of treating any disorders by administering variants of any polypeptides." (Examiner's emphasis). The amendment of claim 1 to refer to "antibody" polypeptides is believed to address, in part, this basis of the rejection. As to treating disorders generally, Applicant submit that the level of skill in the art at the time of filing in 1999 was such that a variety of different disorders treatable by many different therapeutic antibodies were known. Examples of such disorders and antibodies included the Rituxan®, Herceptin®, Campath-1H, anti-Id, anti-CD19, and anti-CD40 antibodies identified in Eccles and Tutt. Variant forms of such antibodies could have been made at the time of filing (and the Examiner acknowledges that the specification discloses antibody variants with improved ADCC function). Those variant antibodies could have been used to treat disorders such as those said to be treated in Eccles and Tutt. Hence, Applicant submits that the disclosure of the present application coupled with the level of skill in the art at the time of filing would have enabled the presently claimed method of treating disorders by administering antibody variants.

Applicant submits that the claimed invention is enabled by the disclosure. Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph – Written Description

Claims 1, 5-11 and 14 are rejected under 35 USC Section 112, first paragraph as failing to satisfy the written description requirement thereof.

Without acquiescing in the rejection, and, in order to expedite prosecution, non-rejected claim 2, concerning antibody variants, is incorporated into claim 1, thus obviating the rejection.

Reconsideration and withdrawal of the Section 112, first paragraph written description rejection is respectfully requested.

Statement of Related Cases

Applicant asks the Examiner to consider related US Application No. 09/713,425 with respect to the above application. Other related applications or patents for consideration have been cited in IDS(s) by US patent No or US-A publication No. Consideration of the related cases is respectfully requested.

Applicant believes that this application is now in condition for allowance, and looks forward to early notification to that effect.

This response/amendment is submitted with a petition for a one month extension of time and fees. In the unlikely event that this document is separated or if further fees are required, Applicant petitions the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,
GENENTECH, INC.

Date: 2-13-06 By: _____

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